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ARTICLE

Sabatolimab (MBG453) model-informed drug development for dose selection in patients with myelodysplastic syndrome/acute myeloid leukemia and solid tumors

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Abstract

Sabatolimab is a novel immunotherapy with immuno-myeloid activity that targets T-cell immunoglobulin domain and mucin domain-3 (TIM-3) on immune cells and leukemic blasts. It is being evaluated for the treatment of myeloid malignancies in the STIMULUS clinical trial program. The objective of this analysis was to support the sabatolimab dose-regimen selection in hematologic malignancies. A population pharmacokinetic (PopPK) model was fit to patients with solid tumors and hematologic malignancies, which included acute myeloid leukemia, myelodysplastic syndrome (including intermediate-, high-, and very high-risk per Revised International Prognostic Scoring System), and chronic myelomonocytic leukemia. The PopPK model, together with a predictive model of sabatolimab distribution to the bone marrow and binding to TIM-3 was used to predict membrane-bound TIM-3 bone marrow occupancy. In addition, the total soluble TIM-3 (sTIM-3) kinetics and the pharmacokinetic (PK) exposure-response relationship in patients with hematologic malignancies were examined. At intravenous doses above 240 mg Q2w and 800 mg Q4w, we observed linear PK, a plateau in the accumulation of total sTIM-3, and a flat exposure-response relationship for both safety and efficacy. In addition, the model predicted membrane-bound TIM-3 occupancy in the bone marrow was above 95% in over 95% of patients. Therefore, these results support the selection of the 400 mg Q2w and 800 mg Q4w dosing regimens for the STIMULUS clinical trial program.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Sabatolimab, a novel immunotherapy targeting TIM-3, is being investigated for the treatment of myeloid malignancies in the STIMULUS clinical trial program.

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The pharmacokinetics (PK) of sabatolimab have been reported in a first-in-human phase I/II study of sabatolimab alone or in combination with spartalizumab in patients with advanced solid tumors.

WHAT QUESTION DID THIS STUDY ADDRESS?

The objectives of this analysis were to report PK, receptor occupancy, and exposure-response data from patients with advanced solid tumors and hematologic malignancies (acute myeloid leukemia [AML], myelodysplastic syndrome [MDS], and chronic myelomonocytic leukemia) treated with sabatolimab as a single agent or in combination with hypomethylating agents and/or spartalizumab.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

In this report, 400 mg Q2w and 800 mg Q4w provided similarly high levels of TIM-3 engagement. No clear relationship was seen between sabatolimab steady-state exposure and safety/efficacy at the doses tested.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

These results support clinical development of the sabatolimab 400 mg Q2w and 800 mg Q4w dosing regimens for higher-risk patients with MDS and AML in the STIMULUS clinical trial program.

INTRODUCTION

T-cell immunoglobulin domain and mucin domain-3 (TIM-3) is an immuno-myeloid regulator expressed on multiple immune cells and leukemic stem cells.[1–4] TIM-3 helps regulate innate and adaptive immune responses.[1,2] TIM-3, an inhibitory cell surface receptor, may suppress macrophage function, natural killer cell cytotoxicity and cytokine production, dendritic cell activation, and chemokine secretion.[1,2,5–8] Additionally, TIM-3 is expressed on leukemic stem cells (LSCs) and blasts but not on normal hematopoietic stem cells[2]; the interaction of TIM-3 and its ligand galectin-9 forms an autocrine loop promoting LSC self-renewal.[9] Thus, both the immune regulatory and leukemic roles of TIM-3 make it a promising novel target in myeloid malignancies.[10–12]

Sabatolimab (MBG453) is a high-affinity, humanized, IgG4 (S228P) antibody targeting the TIM-3 receptor on both immune and leukemic cells,[1,13,14] as well as the circulating, soluble TIM-3 (sTIM-3) that is shed from the cell surface.[2] Sabatolimab is a novel immunotherapy under investigation for the treatment of myeloid malignancies.[15] It has shown immuno-myeloid activity with a potential dual mechanism against acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Sabatolimab binding to TIM-3 on immune cells may reactivate the immune system, boosting its ability to eliminate LSCs and blasts.[1,14,15] Sabatolimab may also directly target TIM-3 on leukemic blasts, suppressing the growth of cancer cells.[1,14] A phase Ib study (NCT03066648) investigating the safety, tolerability, and efficacy of sabatolimab + hypomethylating agents (HMAs) in patients with high-risk/very high-risk MDS and newly diagnosed AML demonstrated a tolerable safety profile with few clinically significant, possible immune-mediated adverse events (AEs) regardless of the relationship to study treatment. Durable clinical benefit was demonstrated with promising remission rates including in patients with adverse risk disease.[15] Further phase II/III studies of sabatolimab + HMA are underway as part of the STIMULUS clinical trial program.[16] Dose regimen selection was critical to initiate the phase II/III STIMULUS studies.

Immuno-oncology therapy is often safe over a large dose range, challenging the traditional cytotoxic dose-selection paradigm of selecting the recommended phase II dose to be the maximum tolerated dose (MTD).[17–20] For sabatolimab, the MTD was not reached in the first-in-human study as sabatolimab was safe and well-tolerated over a 60-fold dose range (20 mg Q2w to 1200 mg Q2w) in patients with advanced solid tumors.[13] Thus far, no well-established biomarker of the downstream sabatolimab effect has been identified for informing dose selection. Therefore, to guide dose selection, we used pharmacokinetics (PK) and sTIM-3 to identify doses where there is (1) saturation of the target mediated drug disposition (TMDD), (2) saturation of the soluble target, and (3) predicted saturation of the membrane-bound TIM-3 (mTIM-3) in the bone marrow. We then evaluated the exposure-response relationship for both safety and efficacy, noting that a flat relationship for exposure-safety

and exposure-efficacy is consistent with TIM-3 saturation. The analysis provided a holistic approach, enabling the selection of the recommended dose regimens for the phase II/III studies in the STIMULUS trial program in patients treated with sabatolimab as a single agent or in combination with HMAs or spartalizumab (programmed death-1 [PD-1] inhibitor).

METHODS

Patient population

The PK data were pooled from two studies: a phase I/II study in patients with advanced solid tumors (NCT02608268)[21] and a phase Ib study in patients with hematologic malignancies, namely AML, MDS, or chronic myelomonocytic leukemia (CMML), who were ineligible for intensive chemotherapy (NCT03066648).[21] Both studies were designed, implemented, and reported in accordance with the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice, applicable local regulations, and the Declaration of Helsinki. The protocols and proposed informed consent forms were reviewed and approved by properly constituted institutional review boards/independent ethics committees/research ethics boards before study start.

In both studies, patients had to be greater than or equal to 18 years old, have Eastern Cooperative Oncology Group performance status less than or equal to 2, and provide written informed consent. Patients with solid tumors had to have histologically documented advanced/metastatic tumors, a biopsy-amenable disease site, and be a tumor biopsy candidate willing to undergo the procedure at screening and during the study. Patients with hematologic malignancies had to be ineligible for intensive chemotherapy and be a serial bone marrow aspirate and/or biopsy candidate willing to undergo the procedure at screening, during, and at the end of study therapy. Additional inclusion requirements from both studies are listed in the Appendices S1 and S2.[21]

Patients with solid tumors received sabatolimab intravenous (i.v.) 80–1200 mg Q2w/Q4w or sabatolimab i.v. 20–800 mg Q2w/80–1200 mg Q4w + spartalizumab. Patients with hematologic malignancies received either sabatolimab i.v. 400 or 1200 mg Q2w, sabatolimab i.v. 240, 400, or 800 mg Q4w + HMA (decitabine or azacitidine), or sabatolimab i.v. 160, 240, or 400 mg Q2w + spartalizumab ± decitabine (Figure S1). The data cutoff dates were March 9, 2020, for the solid tumor study, and June 25, 2020, for the hematologic malignancies study.

Data collection and sampling

Samples to assess PK properties of sabatolimab were collected from all enrolled patients throughout and at the end of treatment (Figure 1). Sabatolimab PK concentration was quantified by liquid chromatography mass spectrometry with lower limit of quantification (LLOQ) of 1 μg/mL (6.8 nM). Total sTIM-3 concentration was quantified by an enzyme linked immunosorbent assay in human serum with LLOQ of 1.02 ng/mL (40 pM).

Total sabatolimab (free + sTIM-3-bound) and total sTIM-3 (free + sabatolimab-bound) serum concentration data from patients with solid tumors and hematologic malignancies were analyzed.

Modeling and simulation strategy for PK and TIM-3 occupancy

Figure 2 shows the framework for interpreting the PK and TIM-3 data. Cells in the bone marrow express mTIM-3 on their cell membrane. These cells shed sTIM-3, which can be detected in the blood.[2] In the blood, after sabatolimab administration, it binds to sTIM-3 to form a complex. The bone marrow sabatolimab concentration is assumed to be directly proportional to the circulating concentration, scaled by a biodistribution coefficient.[22] In the bone marrow, sabatolimab can bind to mTIM-3. With this model, there are three ways in which we can assess target engagement: PK linearity, plateau in sTIM-3, and predicted mTIM-3 occupancy in bone marrow.

PK linearity

Like other monoclonal antibodies,[23–25] there are two general paths for sabatolimab elimination: a nonspecific mode (endocytosis) and a target-mediated mode (sabatolimab binds to TIM-3 on the cell membrane and is internalized by the cell and degraded in the lysosome). These two processes give rise to nonlinear PK because, at low doses, both routes are active, but at sufficiently high doses, the membrane-bound target is saturated, clearance is dominated by endocytosis, and the PK appears linear. Therefore, the observation of linear PK is consistent with mTIM-3 saturation at higher doses. Later, we describe a nonlinear PopPK model to define this process.

Plateau in sTIM-3

Like other monoclonal antibodies with soluble targets,[25] sabatolimab binding to sTIM-3 increases the half-life of

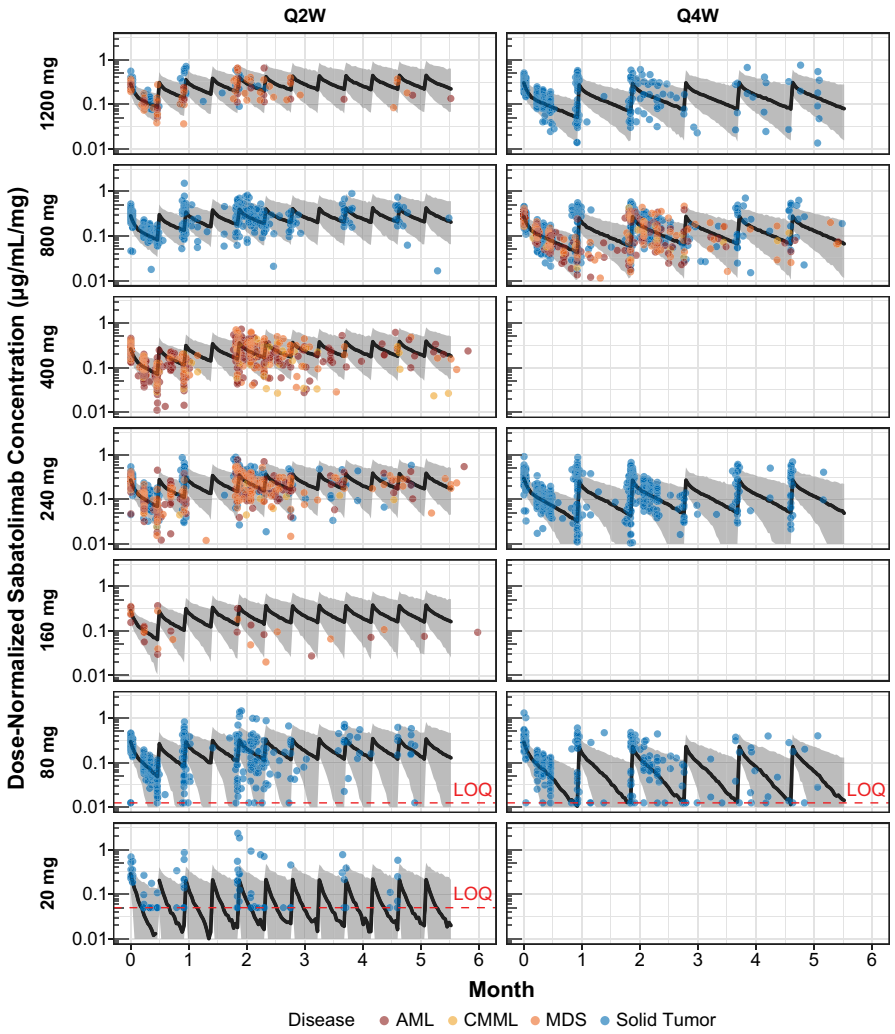

FIGURE 1 Time-course of dose-normalized sabatolimab concentrations from both observation (circles) and simulation (curves and shaded regions). The shaded region shows the 5%–95% prediction interval. The color of the circle indicates patients with hematologic malignancies (AML, MDS, or CMML) or solid tumors and the panels indicate different dosing schedules. Patients with hematologic malignancies were analyzed in the exposure-response analysis. LOQ lines are only shown at 20 and 80 mg doses because we are plotting dose-normalized PK and at higher doses, the LOQ lines fall below the *x*-axis. AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; LOQ, limit of quantification; MDS, myelodysplastic syndrome; PK, pharmacokinetics; Q2W, every 2 weeks; Q4W, every 4 weeks.

sTIM-3, leading to an accumulation of total sTIM-3 (free sTIM-3 + drug-sTIM3 complex). This accumulation increases with dose until almost all of the sTIM-3 is bound, at which point it cannot accumulate further and is said to be saturated. Thus, a plateau in the sTIM-3 indicates saturated sTIM-3 in circulation. Although sTIM-3 accumulates due to drug binding, most of the increased sTIM-3 is inactive.

Predicted mTIM-3 occupancy in bone marrow

We also use the PopPK model to simulate drug distribution into the bone marrow and drug binding to mTIM-3, to predict bone marrow target occupancy. The modeling approach is described in more detail below.

Population PK model

The PopPK model, fit to all patients (both solid tumors and hematologic malignancies), was a two-compartment TMDD model with Michaelis–Menten approximation and i.v. dosing. The ordinary differential equations describing the model are shown below. *CL* is clearance from the central compartment, *Q* is the intercompartmental clearance, *V* is the central volume, V_2 is the peripheral volume, V_m and K_m are the Michaelis–Menten constants for describing nonlinear elimination, *C* is the free drug concentration, and *A* is the drug amount in the peripheral compartment. All parameters were fit to the data, except for K_m (fixed at 0.074 µg/mL [0.5 nM]), based on prior sTIM-3 kinetics modeling, described below. K_m was fixed because it was not estimable from only the PK data.

$$k_{el} = \frac{CL}{V}$$

$$k_{12} = \frac{Q}{V}$$

$$k_{21} = \frac{Q}{V_2}$$

$$\frac{dC}{dt} = -k_{el} \cdot C - \frac{V_m \cdot C}{K_m + C} - k_{12} \cdot C + k_{21} \cdot C + \text{Dose}_{iv}(t)$$

$$\frac{dA}{dt} = k_{12} \cdot C \cdot V - k_{21} \cdot A$$

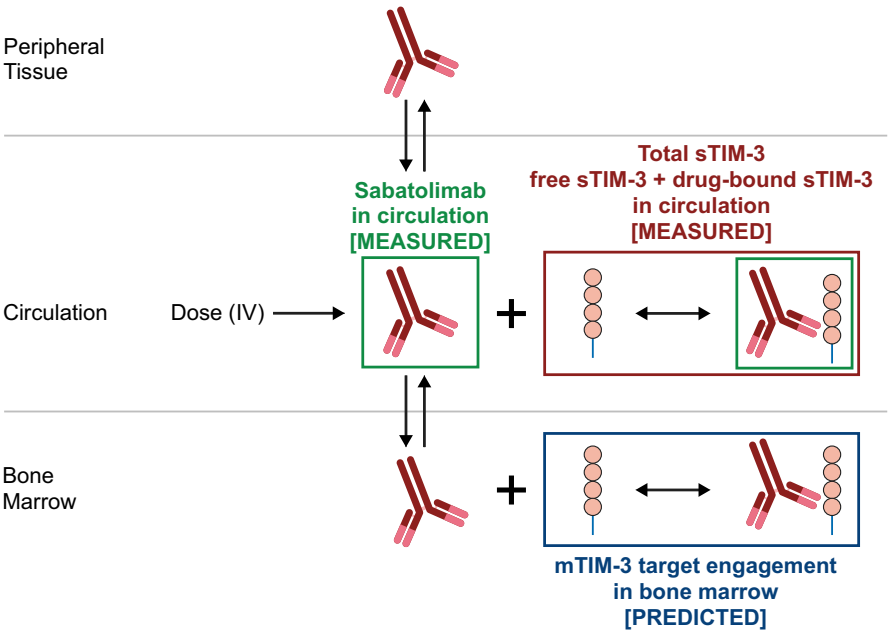

FIGURE 2 Modeling framework to interpret the PK and TIM-3 data. Sabatolimab distributes to the peripheral tissue, including the bone marrow, and binds to the mTIM-3 and sTIM-3. Total sTIM-3 is measured and includes the free sTIM-3 and the sabatolimab-bound sTIM-3. mTIM-3 engagement in tumors is predicted using a binding model of sabatolimab to sTIM-3. IV, intravenous; mTIM-3, membrane-bound TIM-3; PK, pharmacokinetics; sTIM-3, soluble TIM-3; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

Lognormal random effects were added to all parameters, except for K_m and Q. Monolix generally works best when random effects are included for all parameters; however, during model building, we found that the variability of the random effects on K_m and Q were not well estimated (Monolix Stochastic Approximation Expectation Maximization estimates for these parameters did not converge), hence random effects on K_m and Q were removed from the model. All random effects were uncorrelated, except for a V and CL correlation. The residual error model for the sabatolimab concentration was a combined model of constant plus proportional error (equation below). LIDV is the measurement for sabatolimab, C is the model prediction, a and b are the constant and proportional components of the error variance, and e is a normally distributed random variable with mean 0 and variance 1.

$$\mathrm{LIDV} = C + \sqrt{a^2 + (b \cdot C)^2} \cdot e$$

Data below the LLOQ were flagged using the CENS column and were treated as below limit of quantification (BLOQ) values in the Monolix dataset. Monolix integrates all possible PK values BLOQ when calculating the likelihood contribution from these data points.[26]

For assessing the covariate effects on PK, the full covariate model approach was used[27–29] where only one model was evaluated, without the need to select covariates for inclusion/exclusion. This approach was advantageous in that it was simple, efficient (only one model was evaluated), and it did not require multiple comparisons. The main purpose was to evaluate if any covariate effects were large enough to merit dose adjustment based on these covariates, and this could be done efficiently with a single model. As a sensitivity analysis, we also removed all covariates that were not statistically significant from the model and assessed the change in the model parameters.

The prespecified covariates that were assessed were impact of baseline weight on V, V_2, and CL, and the impact of disease and comedication with spartalizumab on CL.

For patient i, the formulas of CL, V, and V_2 are listed below:

$$CL_i = CL_{\mathrm{pop}} \cdot \exp\left[\eta_{CL,i} + \beta_{CL,\mathrm{WT0}} \cdot \log\left(\frac{\mathrm{WT}_{0,i}}{\mathrm{WT}_{0,\mathrm{median}}}\right) + \beta_{CL,\mathrm{HASPDR}} \cdot \mathrm{HASPDR}_i + \beta_{CL,\mathrm{MDS}} \cdot \mathrm{MDS}_i + \beta_{CL,\mathrm{AML}} \cdot \mathrm{AML}_i + \beta_{CL,\mathrm{CMML}} \cdot \mathrm{CMML}_i\right]$$

$$V_i = V_{\mathrm{pop}} \cdot \exp\left[\eta_{V,i} + \beta_{V,\mathrm{WT0}} \cdot \log\left(\frac{\mathrm{WT}_{0,i}}{\mathrm{WT}_{0,\mathrm{median}}}\right)\right]$$

$$V_{2i} = V_{2\mathrm{pop}} \cdot \exp\left[\eta_{V2,i} + \beta_{V2,\mathrm{WT0}} \cdot \log\left(\frac{\mathrm{WT}_{0,i}}{\mathrm{WT}_{0,\mathrm{median}}}\right)\right]$$

Here, $\mathrm{WT}_{0,i}$ is the baseline weight of patient i, $\mathrm{WT}_{0,\mathrm{median}}$ is the median baseline weight of the patient population. CL_{pop}, V_{pop}, and $V_{2\mathrm{pop}}$ are population fixed effects, and $\eta_{CL,i}$, $\eta_{V,i}$, and $\eta_{V2,i}$ are random effects. The effect of weight on CL, V, and V_2 are given by $\beta_{CL,\mathrm{WT0}}$, $\beta_{V,\mathrm{WT0}}$, and $\beta_{\mathrm{V2,WT0}}$. The reference patient has the solid tumor indications and patients with hematologic malignancies are described by the indicator variables AML_i, MDS_i, and CMML_i, with covariate effects on CL given by $\beta_{CL,\mathrm{AML}}$, $\beta_{CL,\mathrm{MDS}}$, and $\beta_{CL,\mathrm{CMML}}$, respectively. The effect of receiving spartalizumab is described by the indicator variable HASPDR (short for "this patient HAS received PDR001 [spartalizumab, anti PD-1 mAb]") with covariate effect of CL of $\beta_{CL,\mathrm{HASPDR}}$.

Patients with hematologic malignancies were given decitabine as the only HMA early in the study, but later, patients were assigned to receive azacitidine. This covariate was not prespecified so it was not included in the full model approach. Instead, we examined how the random effect on *CL* changes with treatment to test whether HMA choice affected exposure.

The PopPK model was also used to estimate the terminal half-life in the linear regime, using the analytical expression from the two-compartment model for the terminal slope (β). The linear formula for half-life is used because at the doses of interest, the PK were linear during the dosing interval.

$$\beta = \frac{1}{2}\left(\frac{CL}{V} + \frac{Q}{V} + \frac{Q}{V_2} - \sqrt{\left(\frac{CL}{V} + \frac{Q}{V} + \frac{Q}{V_2}\right)^2 - 4 \cdot \frac{CL}{V} \cdot \frac{Q}{V_2}}\right)$$

The sTIM-3 data + model

For the total sTIM-3 concentration data in serum, a quasi-steady-state TMDD model was previously fit to the PK and sTIM-3 data of the patients with solid tumors.[13] This model described the data well. The binding affinity was estimated to be $K_{ss}=0.2$ nM, which was similar to the quasi-steady-state binding constant measured from cell-based assays in vitro ($K_{ss}=0.5$ nM).

This model was not updated when we pooled patients with hematologic malignancies because only high-dose data where the sTIM-3 reached its plateau were collected; this was not expected to change the results or the K_{ss} estimate. Therefore, in this paper, we provide simulations of the previous model, overlaid with both the solid tumor and hematologic malignancy data.

Model simulation to predict steady-state trough plasma concentration and mTIM-3 occupancy in bone marrow

We bootstrapped the covariates from the hematologic malignancy subpopulation to simulate steady-state trough plasma concentration ($C_{trough,ss}$). We subsequently predicted the membrane-bound receptor occupancy (RO) in the bone marrow at steady-state at the lowest drug concentration (just before the next dose [i.e., trough]), for all TIM-3-expressing cells, using the following equation.[30]

$$RO \approx \frac{B \cdot C_{trough,ss}}{B \cdot C_{trough,ss} + T_{acc} \cdot K_{ss}}$$

B is the biodistribution coefficient,[22] which denotes the ratio of the drug concentration in the bone marrow interstitial fluid to the drug concentration in plasma. B was calculated based on the assumption that in bone marrow, the drug concentration is 7% of circulation[22] and that the fraction of bone marrow that is interstitial fluid is 16.7%.[31] Therefore, the fraction of drug in the bone marrow interstitial fluid would be 7%/16.7% = 42%. In a sensitivity analysis, $B=21\%$ was also explored. $C_{trough,ss}$ is simulated from the PopPK model. T_{acc} is the fold change in the mTIM-3, assumed to be 1 (i.e., no change in TIM-3 expression upon binding to drug), because unlike sTIM-3 that accumulates when bound to sabatolimab, mTIM-3 is not expected to accumulate upon drug binding. In a sensitivity analysis, $T_{acc}=0.5$ was also explored, which corresponds to faster internalization of TIM-3 upon sabatolimab binding. $K_{ss}=0.5$ nM is the quasi-steady-state binding constant for mTIM-3, estimated from an in vitro binding assay and similar to the quasi-equilibrium K_d for sTIM-3 (0.2 nM). Application of the above equation for RO required the assumption that tumor tissue was homogenous and that sabatolimab concentration was in excess to the TIM-3 concentration in the tumor.

Exposure-response relationship

Exposure-response analyses were conducted using clinical response and PK data from patients with hematologic malignancies treated with sabatolimab 240 mg Q2w, 400 mg Q2w, and 800 mg Q4w in combination with decitabine/azacitidine. The relationship between sabatolimab exposure and efficacy was evaluated in two ways. First, we performed a linear regression to assess the relationship between $C_{trough,D28}$ and the best percent reduction from baseline in bone marrow blasts. Second, we performed a logistic regression between $C_{trough,D28}$ and the achievement of clinical benefit (defined as complete remission [CR], marrow CR [mCR], CR with incomplete hematologic recovery [CRi], or partial remission [PR] per International Working Group for AML[32] and MDS[33]). Although all patients were assessed to either have clinical benefit or not, the percent reduction in bone marrow blasts was computed only for the subset of patients who started with a baseline level of greater than 5% blasts and had at least one follow-up bone marrow biopsy.

In the exposure-response analysis, the values of maximum plasma concentration (C_{max1}; C_{max} after first dose) and $C_{trough,D28}$ were simulated for each patient under the assigned dosing regimen using the individual conditional mode estimate of that patient's PK parameters. We report PK parameters from the first 28 days instead of steady-state to reduce confounding risk as response has been shown to impact long-term exposure for PD-1 checkpoint inhibitors.[34]

To evaluate the relationship between sabatolimab exposure and AEs, patients were divided into four exposure quartile groups based on sabatolimab C_{max1}. Potential treatment-related AEs (as determined by the investigator) were assessed across sabatolimab exposure categories.

To assess fixed versus bodyweight scaled dosing regimens, the sabatolimab trough concentrations at steady-state were simulated for patients with solid tumors ($n=1000$) using the model for 800 mg and 11 mg/kg (800 mg/70 kg) given every 2, 3, or 4 weeks. All patients were expected to be at steady-state by month 6. The median and 95% prediction interval values were plotted.

RESULTS

Patients

Analyses included 444 patients (252 with solid tumors, and 192 with hematologic malignancies; Figure S2). Of these, 159 patients received sabatolimab monotherapy (133 with solid tumors and 26 with hematologic malignancies), 130 received sabatolimab + spartalizumab (119 with solid tumors and 11 with hematologic malignancies), 55 received sabatolimab + azacitidine (all with hematologic malignancies), and 100 received sabatolimab + decitabine ± spartalizumab (all with hematologic malignancies). Demographic data for phase I study on patients with solid tumors were previously published[13] and the phase Ib study on patients with hematologic malignancies are presented in Table S1.

PK and TIM-3 Modeling results

Population PK

Simulation of 1000 patients, using the model parameter estimates (including residual error) is shown with the data overlaid in Figure 1, and the model parameters are summarized in Table 1. Goodness of fit plots (Figure S3) demonstrated the final model fit the data well. The statistically significant covariates ($p<0.05$) were weight (on CL, V, and V_2), and the MDS indication on CL, relative to solid tumors. The MDS effect reduced CL by $\exp(\beta_{CL,MDS})=14\%$, although the other indications (AML and CMML) did not have a statistically significant effect. No statistically significant effect of spartalizumab was observed on CL, and no difference between the HMAs was detected (Figure S4). Removing the covariates that were not statistically significant from the model (all but weight and the effect of MDS on CL) had a minimal impact on the model parameters. All model parameters changed by less than or equal to 10% from their original value. The parameter that changed the most was the impact of the MDS indication on CL ($\beta_{CL,MDS}$), which changed from −0.149 to −0.164, which meant that patients with MDS had a 16.4% reduction in CL instead of 14.9%.

In Figure 3, we simulate the PopPK model, plot the dose-normalized $C_{trough,ss}$ over a range of doses, and overlay the observed data. The focus is on $C_{trough,ss}$ (rather than $C_{avg,ss}$ or $C_{max,ss}$) because the goal was to maintain TIM-3 saturation over the entire dosing interval. At lower doses (≤80 mg Q2w or ≤240 mg Q4w), the PK were nonlinear, with faster elimination at lower concentrations suggesting a potential for TMDD. The PK appeared linear with an approximate proportional dose-exposure relationship at doses greater than or equal to 240 mg Q2w and greater than or equal to 800 mg Q4w.

The estimated half-life of sabatolimab was 18.7 days at linear PK dose levels. Sabatolimab accumulation was observed with repeated administrations and, for the Q2w regimen, area under the concentration curve for a dosing interval (AUC_{tau}) during cycle 3 ranged from 1.01- to 2.78-fold higher than during cycle 1. The 800 mg Q4w dose had similar $C_{avg,ss}$ to 400 mg Q2w. Time-dependent CL was investigated in patients with hematologic malignancies by viewing the model residuals as a function of time and stratified by response type, with no trends observed.

sTIM-3 kinetics

In all patients, a plateau in sTIM-3 was achieved with sabatolimab doses greater than or equal to 240 mg Q2w and greater than or equal to 800 mg Q4w, demonstrating a high degree of target engagement (Figure 4). At the lowest doses (20 mg Q2w and 80 mg Q4w) it was clear that sTIM-3 does not stay engaged throughout the dosing interval.

Prediction of mTIM-3 occupancy in bone marrow

The results from the population simulation of 1000 patients, using the model parameter estimates (including residual error) for predicted mTIM-3 occupancy in the bone marrow, are shown in Figure 5.[35] The model predicted that in greater than or equal to 95% of patients at $C_{trough,ss}$, 400 mg Q2w and 800 mg Q4w gave greater than 95% membrane-bound RO (Figure 5). Based on our sensitivity analysis, even with lower bioavailability ($B=21\%$) or less accumulation ($T_{acc}=0.5$), greater than 95% of patients were still expected to have greater than 95% TIM-3 occupancy in the bone marrow (Figure S5).

TABLE 1 Model parameters.

Type	Parameter	Unit	Values	SE	RSE, %	Eta-shrinkage	*p* value
Fixed effect	CL	L/h	0.0103	0.000443	4.29		
Fixed effect	V	L	3.59	0.048	1.34		
Fixed effect	Q	L/h	0.0353	0.00236	6.67		
Fixed effect	V_2	L	2.38	0.0703	2.95		
Fixed effect	V_m	μg/mL/h	0.0197	0.00162	8.23		
Fixed effect	K_m	μg/mL	0.074[a]				
Random effect[b]	ω_{CL}	–	0.473	0.0184	3.88	0.16	
Random effect[b]	ω_V	–	0.23	0.00977	4.24	0.23	
Random effect[b]	ω_{V2}	–	0.338	0.0299	8.85	0.63	
Random effect[b]	ω_{Vm}	–	0.641	0.0673	10.5	0.81	
Correlation	Corr_V_CL	–	0.634	0.0431	6.79		
Error	a	–	1.41	0.0853	6.05		
Error	b	–	0.19	0.00282	1.49		
Covariate effect[c]	$\beta_{CL,HASPDR}$	–	0.0194	0.0506	260		0.7
Covariate effect[c]	$\beta_{CL,AML}$	–	−0.0146	0.0579	396		0.801
Covariate effect[c]	$\beta_{CL,CMML}$	–	−0.0411	0.135	328		0.76
Covariate effect[c]	$\beta_{CL,MDS}$	–	−0.149	0.0647	43.4		0.0213
Covariate effect[d]	$\beta_{CL,WT0}$	–	0.743	0.107	14.4		4.35e-12
Covariate effect[d]	$\beta_{V,WT0}$	–	0.77	0.0537	6.97		<2.2e-16
Covariate effect[d]	$\beta_{V2,WT0}$	–	0.597	0.116	19.5		2.91e-07

Note: WT0 is log (baseline WT/median of baseline WT). Condition number for the covariance matrix was 334,000.

Abbreviations: AML, acute myeloid leukemia; *CL*, clearance; CMML, chronic myelomonocytic leukemia; K_m, kinetic metabolite; MDS, myelodysplastic syndrome; Q, intercompartmental clearance; RSE, relative standard error; SE, standard error; *V*, central volume; V_2, peripheral volume; V_m, Michaelis–Menten constants for describing nonlinear elimination; WT, weight.

[a]The 0.074 μg/mL*1000 ng/μg * 150 kDa = 0.5 nM was fixed.

[b]For the random effects, the standard deviation ω was provided. The coefficient of variation (CV) was calculated by (exp(ω^2)−1).

[c]For these binary covariates, indicating that the patient had received spartalizumab or that the patient had the disease indication of AML, CMML, or MDS instead of a solid tumor, the relative change in *CL* for these covariates was given by exp(β).

[d]For weight effects on *CL*, *V*, and V_2, these covariates were the allometric scaling exponents.

Exposure response

Exposure-efficacy relationship

The relationship between sabatolimab exposure and efficacy was assessed at three dose levels (240 mg Q2w, 400 mg Q2w, and 800 mg Q4w) in 140 patients with hematologic malignancies, in both combination groups (sabatolimab + decitabine/azacitidine). There was no clear relationship between $C_{trough,D28}$ versus the efficacy metrics of percentage of blast cell reduction (Figure 6a) or clinical benefit, defined as CR/mCR/CRi/PR (Figure 6b). The linear regression model suggested a flat relationship between the best blast cell reduction and sabatolimab $C_{trough,D28}$ ($p = 0.41$, for descriptive purpose only) as well as between clinical benefit and sabatolimab $C_{trough,D28}$ ($p = 0.37$, for descriptive purpose only).

Exposure-safety relationship

The PK exposure-safety relationship was evaluated in 137 patients with hematologic malignancies treated with sabatolimab + decitabine or azacitidine categorized into four exposure quartile groups based on C_{max1}. The results showed no major differences in safety across exposure levels (Figure 6c); no relationship was observed between C_{max1} and incidence of potentially treatment-related AEs. Most commonly reported AEs were consistent with those for HMA alone (Table S1)[13,36]; single-agent sabatolimab had a much safer toxicity profile up to 1200 mg Q2w.[13]

Fixed versus body-weight scaled dosing

Simulations of the sabatolimab trough concentration at steady-state are shown in Figure S6 for both fixed and body-scaled dosing. The predicted variability in the sabatolimab trough concentration is comparable for patients receiving either fixed or body-weight scaled dosing.

DISCUSSION

Dose justification for sabatolimab at 400 mg Q2w and 800 mg Q4w

In summary, the 400 mg Q2w and 800 mg Q4w dose regimens were recommended for the STIMULUS clinical

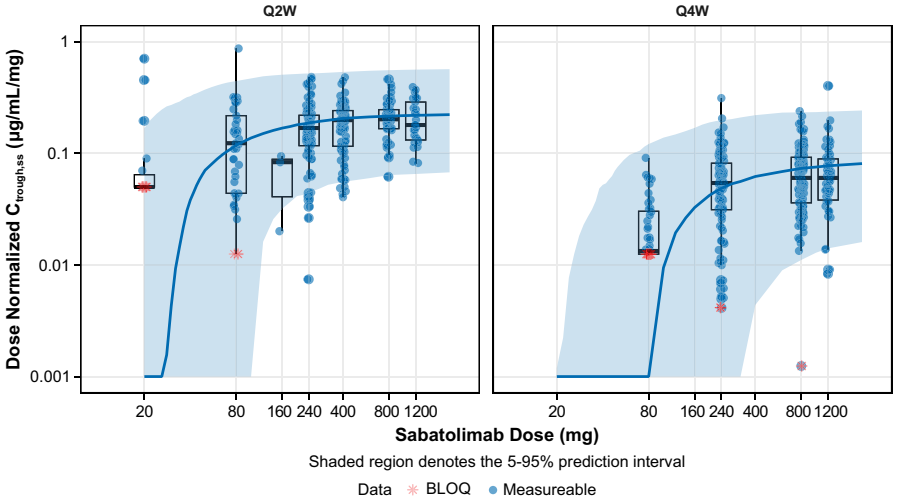

FIGURE 3 Dose-normalized $C_{trough,ss}$ was plotted over a range of doses and PopPK model was simulated. The PK were nonlinear at lower doses and appeared to have an approximate proportional dose-exposure relationship at greater than or equal to 240 mg Q2w and greater than or equal to 800 mg Q4w. Dose-normalized sabatolimab concentrations below 0.001 µg/mL/mg were imputed at 0.001 µg/mL/mg in this plot. BLOQ, below the limit of quantification; $C_{trough,ss}$, trough concentration at steady-state; PK, pharmacokinetic; PopPK, population pharmacokinetic; Q2W, every 2 weeks; Q4W, every 4 weeks.

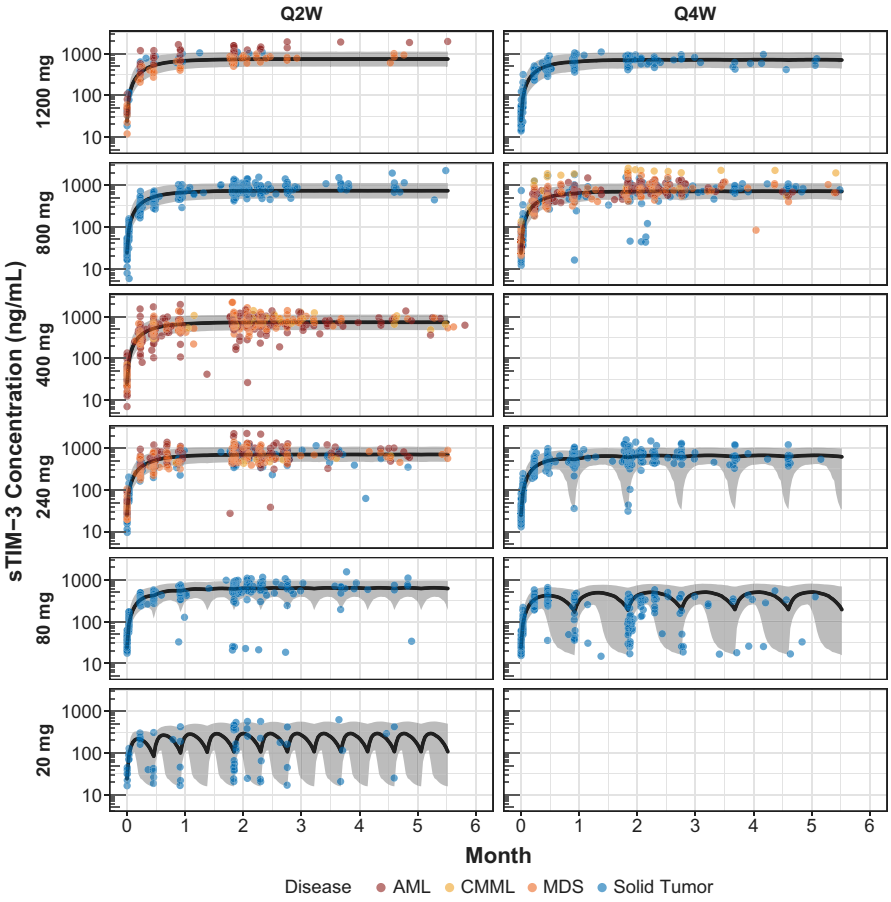

FIGURE 4 Time-course of soluble TIM-3 concentrations from both observation (circles) and simulation (curves and shaded regions). The gray-shaded regions show the 5%–95% prediction interval. The figure shows sabatolimab concentration-time profiles for patients with hematologic malignancies (AML, MDS, and CMML) and solid tumors by dosing schedule. Patients with hematologic malignancies were analyzed in the exposure-response analysis. AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; Q2W, every 2 weeks; Q4W, every 4 weeks; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

trial program, which is currently evaluating the efficacy and safety of sabatolimab combination therapy in patients with higher-risk MDS or AML who are ineligible for intensive chemotherapy or hematopoietic stem cell transplant.[16] The key elements supporting this recommendation were (1) predicted saturation of TIM-3 at these doses, as evaluated by three approaches: linear PK, a plateau in the sTIM-3 profiles, and greater than 95% predicted TIM-3 engagement in the bone marrow in 95% of patients; and (2) a flat exposure-safety and

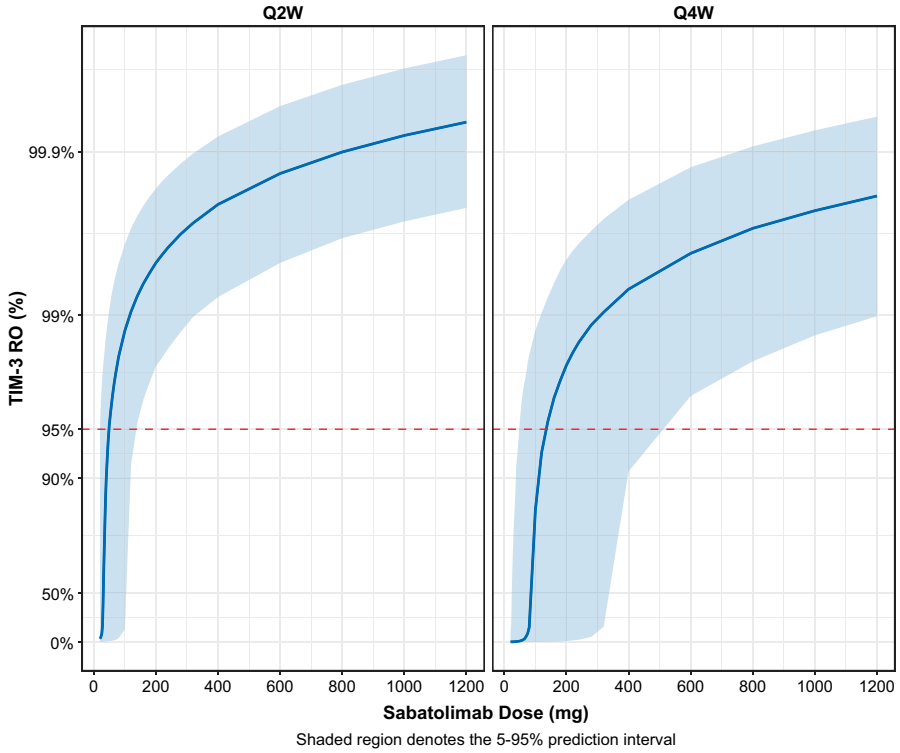

FIGURE 5 Simulated steady-state TIM-3 receptor occupancy in bone marrow compared to baseline. The blue-shaded area denotes 5%–95% prediction interval. Data is plotted on a reverse log transform scale[35] to better visualize receptor occupancy data near 100%. Q2W, every 2 weeks; Q4W, every 4 weeks; RO, receptor occupancy; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

exposure-efficacy relationship at the doses tested in patients with hematologic malignancies.

Similar approach used for dose justification for other biologics

Target engagement data for dose justification has been used for other biologics. Linear PK as a sign that the receptor-mediated elimination of the drug has been saturated and there is a high level of target engagement was previously used for cetuximab (anti-EGFR).[37] Modeling of the soluble target data to predict free soluble target levels was used for justifying the dose of omalizumab (anti-IgE).[38] Moreover, prediction of the membrane-bound target occupancy was one aspect used in justifying the dose for pembrolizumab (anti-PD-1)[39] and atezolizumab (anti-PD-L1).[40] The two approaches for predicting target engagement of pembrolizumab and atezolizumab differed, with the pembrolizumab team building a minimal physiologically-based pharmacokinetic model to predict occupancy in the tumor and with the atezolizumab team using an approach similar to ours, where a simple algebraic equation that accounts for biodistribution and the target binding affinity could be used to predict target occupancy. We previously showed that this algebraic expression could be derived from a physiologically based model,[30] and so it is expected that both approaches would give similar answers. Predicting the TIM-3 inhibition in the bone marrow relies on some key assumptions: that bone marrow sabatolimab concentrations will be 21%–42% of plasma sabatolimab concentrations, that the drug is in vast excess of the bone marrow TIM-3 levels, and that the bone marrow can be treated as a homogenous tissue.

The degree and duration of TIM-3 inhibition needed for clinical efficacy is unknown. For antagonists, it is typical to target 90%–95% RO (or 5%–10% free target compared to baseline) throughout the dosing interval. For many biologics, including immune checkpoint inhibitors, it has been predicted that all provide greater than or equal to 90% target occupancy.[41] This level of RO has not been validated for TIM-3.

Consideration of dose finding framework

Following the Novartis dose-finding framework,[42] we considered whether other dosing regimens should also be explored in phase II/III trials. We have seen no evidence that safety is related to dose over a large dose range (20 mg Q2w to 1200 mg Q2w). Given the favorable toxicity profile, the solid tumor data allowed the first dose tested in the phase Ib expansion in hematologic malignancies to be a saturating dose of 240 mg Q2w. By leveraging knowledge of the dose-safety relationship in solid tumors, we were able to efficiently test target saturating doses in the clinic. Similar to the sabatolimab approach, PD-1 and PD-L1 checkpoint inhibitors also only explored saturating doses in their phase II/III trials.[43]

Two PD-1 checkpoint inhibitors explored more than one saturating dose level in their pivotal studies: 3 mg/kg and 10 mg/kg Q2w for nivolumab,[44] and 2 mg/kg and

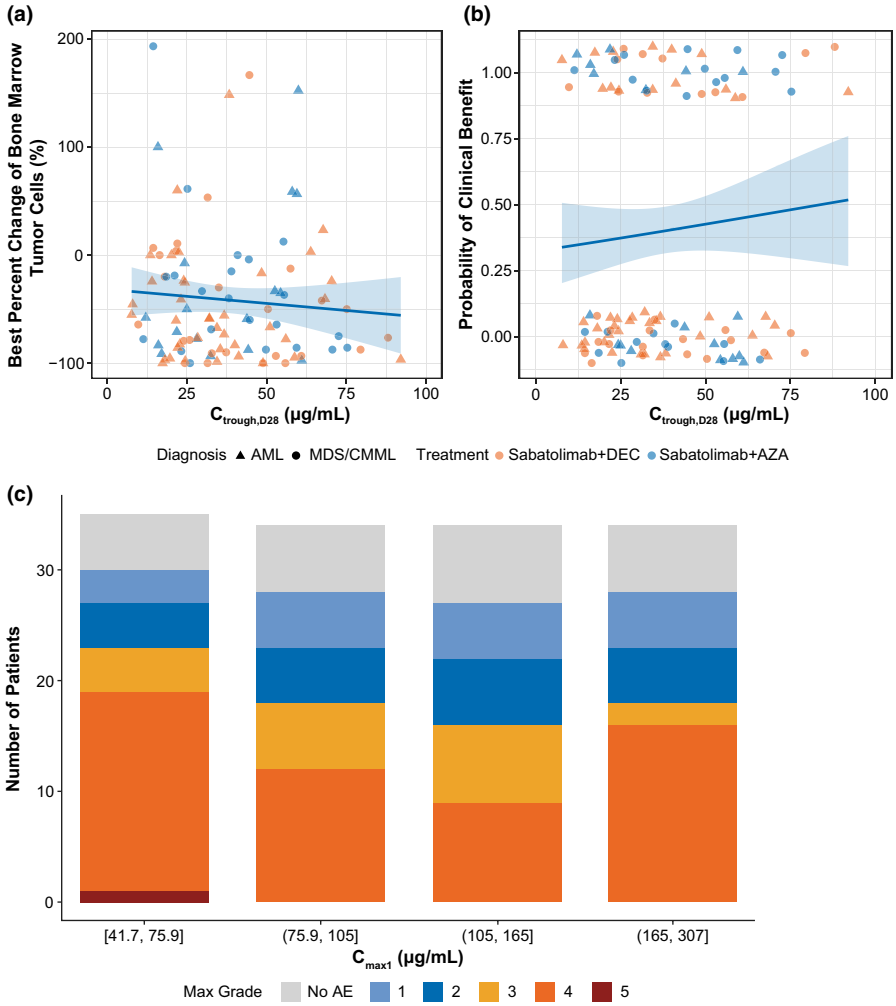

FIGURE 6 PK exposure-response relationship. Relationship between sabatolimab exposure ($C_{trough,D28}$) and (a) best percent blast cell reduction or (b) clinical benefit. (c) Relationship between exposure (C_{max1}) and potentially treatment-related AEs; the segments in the bar represents different maximum AE grades. AE, adverse events; AML, acute myeloid leukemia; AZA, azacitidine; CMML, chronic myelomonocytic leukemia; $C_{trough,D28}$, trough concentration at day 28; C_{max1}, maximum concentration after first dose; DEC, decitabine; PK, pharmacokinetic.

10 mg/kg Q2w/Q3w for pembrolizumab.[45] For these drugs, there was no difference in safety or efficacy between the dose groups observed. Therefore, we believe testing a single saturating dose level of sabatolimab with a flat exposure-safety and exposure-efficacy relationship at 800 mg per cycle (every 4 weeks) is sufficient; two different regimens (400 mg Q2w and 800 mg Q4w) were explored in the respective phase II/III studies.

Covariates considered in PopPK analysis for dose recommendation

Weight was a significant covariate, as often observed for monoclonal antibodies. The exposure variability due to bodyweight, however, depends on the magnitude of the bodyweight effect as a covariate.[46,47] The predicted variability in the sabatolimab trough concentration was comparable for patients receiving fixed or bodyweight-based dosing (Figure S6). Furthermore, the flat exposure-response relationship at the doses tested also indicated a lack of benefit for weight-based dosing. These findings support the choice of a fixed-dose regimen.

The PK were similar across all disease indications in both solid tumors and hematologic malignancies and across all combination therapies (spartalizumab, decitabine, and azacitidine). Although a statistically significant 14.9% reduction in *CL* was observed for patients with MDS, this was not expected to have a clinically significant impact because no exposure-safety or exposure-efficacy relationship was observed at the doses tested and sabatolimab was shown to be safe at doses up to 1200 mg Q2w in the solid tumor trials.

It was expected that there would be no drug–drug interaction because sabatolimab, as an IgG, is primarily eliminated by protein catabolism following endocytosis.[24,25] Therefore, the same sabatolimab dose is proposed for either HMA.

CONCLUSION

In conclusion, 400 mg Q2w and 800 mg Q4w were chosen for further clinical development in higher-risk MDS and AML in the STIMULUS clinical trial program. Sabatolimab was well-tolerated as a single agent at doses up to 1200 mg Q2w, with no MTD identified, and it was

also well-tolerated in combination with decitabine or azacitidine. These dose regimens were supported based on an exposure-safety and exposure-efficacy relationship at the doses tested and the prediction that these doses provide a high degree of TIM-3 engagement.

AUTHOR CONTRIBUTIONS

S.X., A.M.S., and H.S. wrote the manuscript. M.L.R. and H.S. designed the research. M.L.R. and H.S. performed the research. S.X., A.M.S., and N.Z. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

S.X. is a Novartis employee and is a Novartis stockholder. N.Z. was a Novartis employee and was a Novartis stockholder. M.L.R. was a Novartis employee and was a Novartis stockholder. H.S. is a Novartis employee and is a Novartis stockholder. A.M.S. is a Novartis employee and is a Novartis stockholder.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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